SKIN-BASED DNA REPAIR PHENOTYPE FOR CANCER RISK FROM GCR IN GENETICALLY DIVERSE POPULATIONS

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Problem

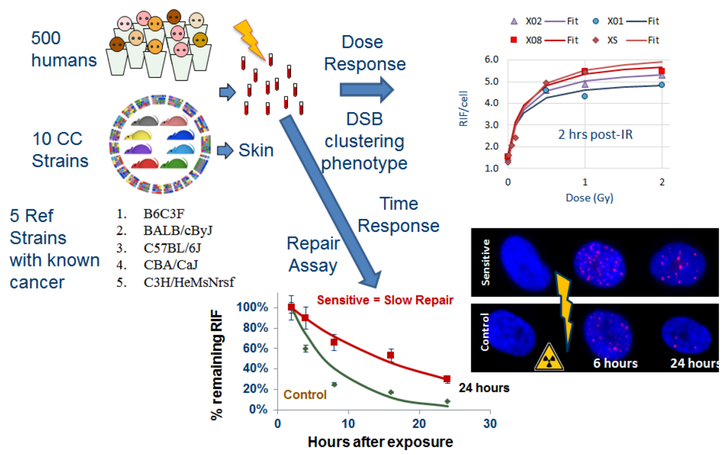
Predicting cancer risk associated with cosmic radiation remains a mission-critical challenge for NASA radiation health scientists and mission planners. Epidemiological data are lacking and risk methods do not take individual radiation sensitivity into account.

Hypothesis

In our approach we hypothesize that genetic factors strongly influence risk of cancer from space radiation and that biomarkers reflecting DNA damage and cell death are ideal tools to predict risk and monitor potential health effects post-flight.

Year 1 – Project Overview

At this workshop, we will be reporting the work we have done over the first 9 months of this proposal. Skin cells from 15 different strains of mice already characterized for radiation-induced cancer sensitivity (B6C3F; BALB/cByJ, C57BL/6J, CBA/CaJ, C3H/HeMsNrsf), and 10 strains from the DOE collaborative cross-mouse model were expanded from ear biopsy and cultivated until Passage 3. On average, 3 males and 3 females for each strain were expanded and frozen for further characterization at the NSRL beam line during the NSRL16C run for three LET (350 MeV/n Si, 350 MeV/n Ar and 600 MeV/n Fe) and two ion fluences (1 and 3 particles per cell).



Experimental Design

Constants

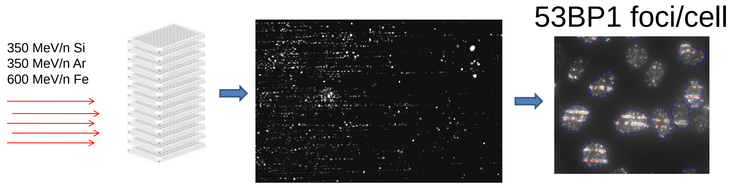
- Strains of animals
- Human PBMC (Year 2 and 3)

Variables

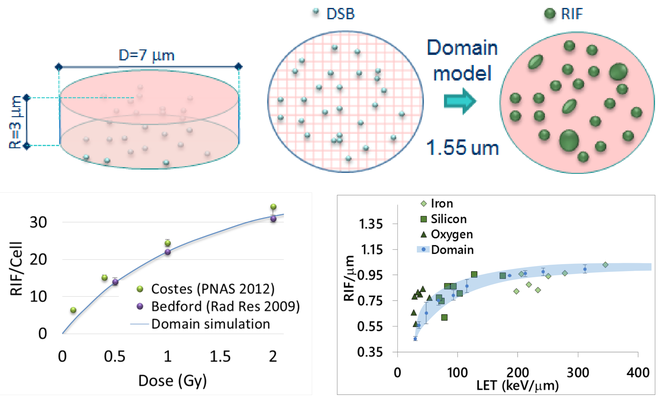
- LET
- Dose
- Time post-IR

Measurements

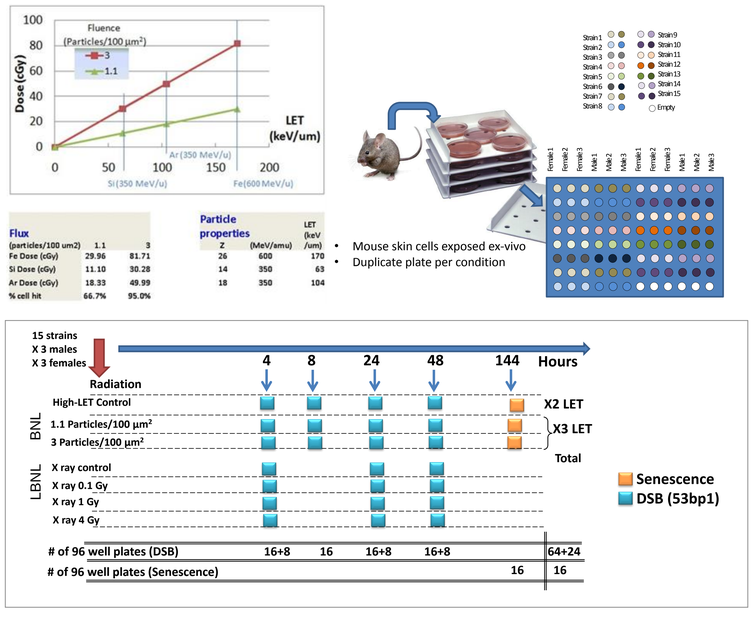
- 53BP1 foci detection as DNA double strand break marker
- Repair Kinetic parameters
  - (power function)
- Foci saturation (Asymptotic fit)
- Foci Background
- 800 cells/condition



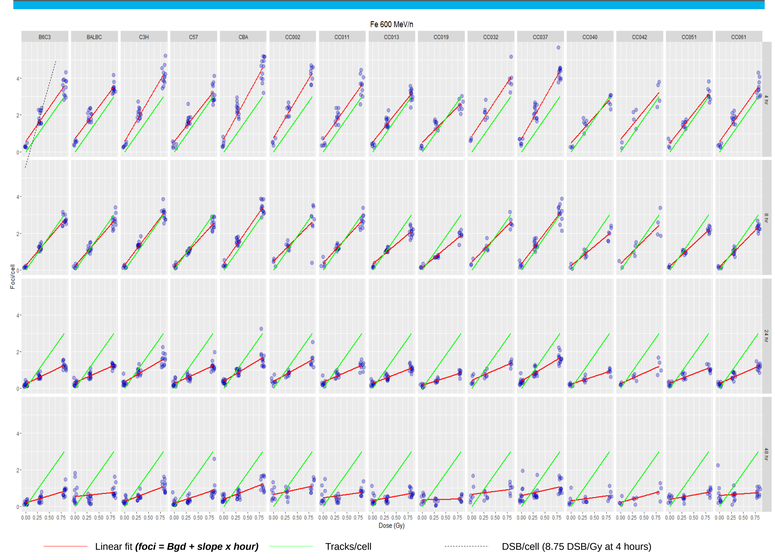
The Model



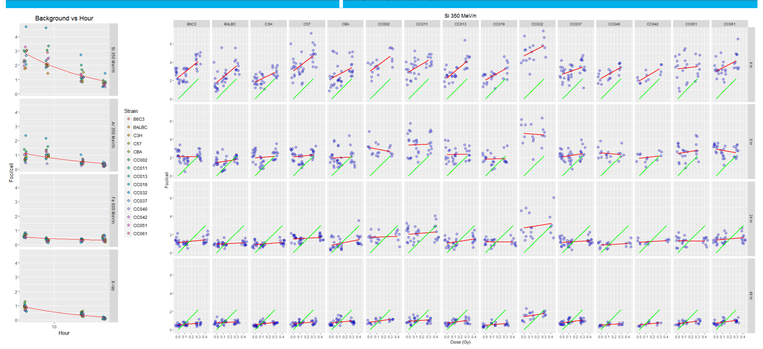
Time and Dose points



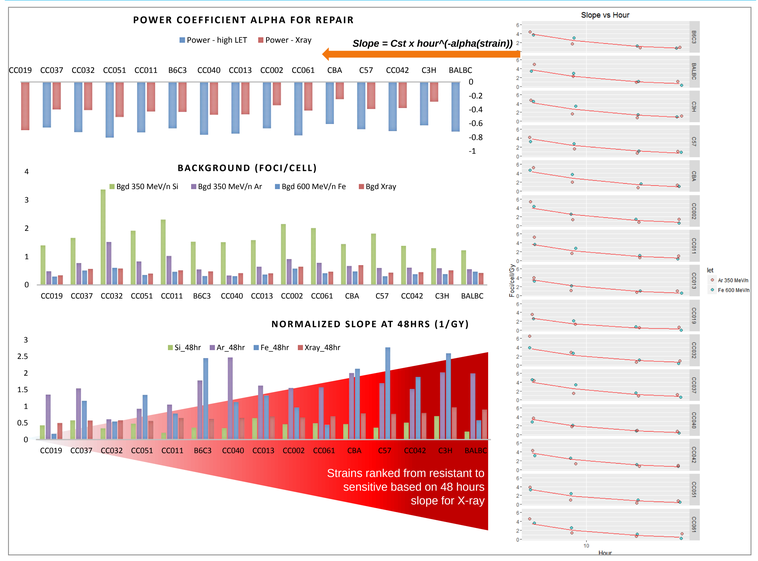
Foci vs Track vs DSB

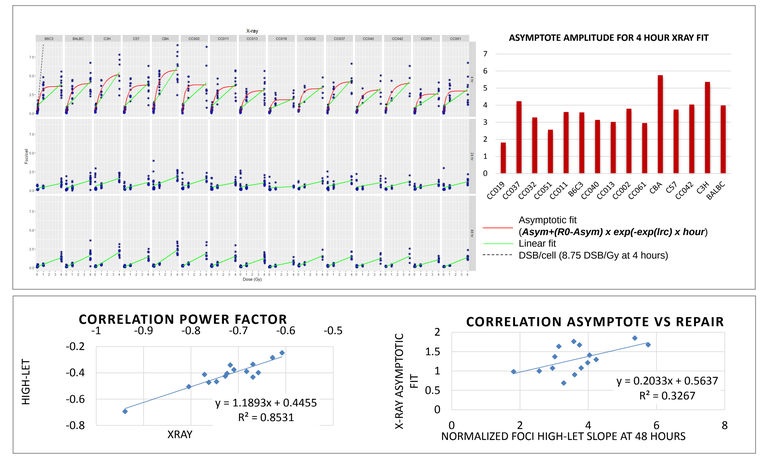


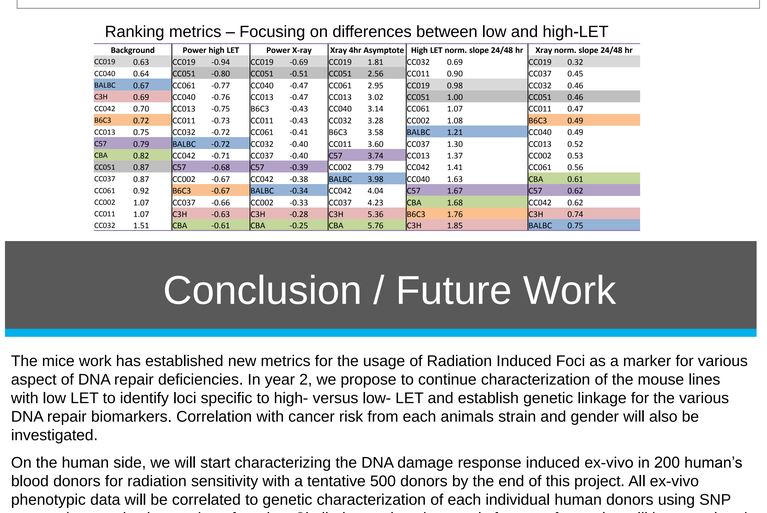
Background issue with non-confluent plates



Strain Radiation Sensitivity







Ranking metrics – Focusing on differences between low and high-LET

Background		Power high LET		Power X-ray		Xray 4hr Asymptote		High LET norm. slope 24/48 hr		Xray norm. slope 24/48 hr	
CC019	0.63	CC019	-0.94	CC019	-0.69	CC019	1.81	CC032	0.69	CC019	0.32
CC040	0.64	CC051	-0.80	CC051	-0.51	CC051	2.56	CC011	0.90	CC037	0.45
BALBC	0.67	CC061	-0.77	CC040	-0.47	CC061	2.95	CC019	0.98	CC032	0.46
C3H	0.69	CC040	-0.76	CC013	-0.47	CC013	3.02	CC051	1.00	CC051	0.46
CC042	0.70	CC013	-0.75	B6C3	-0.43	CC040	3.14	CC061	1.07	CC011	0.47
B6C3	0.72	CC011	-0.73	CC011	-0.43	CC032	3.28	CC002	1.08	B6C3	0.49
CC013	0.75	CC032	-0.72	CC061	-0.41	B6C3	3.58	BALBC	1.21	CC040	0.49
C57	0.79	BALBC	-0.72	CC032	-0.40	CC011	3.60	CC037	1.30	CC013	0.52
CBA	0.82	CC042	-0.71	CC037	-0.40	C57	3.74	CC013	1.37	CC002	0.53
CC051	0.87	C57	-0.68	C57	-0.39	CC002	3.79	CC042	1.41	CC061	0.56
CC037	0.87	CC002	-0.67	CC042	-0.38	BALBC	3.98	CC040	1.63	CBA	0.61
CC061	0.92	B6C3	-0.67	BALBC	-0.34	CC042	4.04	C57	1.67	C57	0.62
CC002	1.07	CC037	-0.66	CC002	-0.33	CC037	4.23	CBA	1.68	CC042	0.62
CC011	1.07	C3H	-0.63	C3H	-0.28	C3H	5.36	B6C3	1.76	C3H	0.74
CC032	1.51	CBA	-0.61	CBA	-0.25	CBA	5.76	C3H	1.85	BALBC	0.75

Conclusion / Future Work

The mice work has established new metrics for the usage of Radiation Induced Foci as a marker for various aspect of DNA repair deficiencies. In year 2, we propose to continue characterization of the mouse lines with low LET to identify loci specific to high- versus low- LET and establish genetic linkage for the various DNA repair biomarkers. Correlation with cancer risk from each animals strain and gender will also be investigated.

On the human side, we will start characterizing the DNA damage response induced ex-vivo in 200 human's blood donors for radiation sensitivity with a tentative 500 donors by the end of this project. All ex-vivo phenotypic data will be correlated to genetic characterization of each individual human donors using SNP arrays characterization as done for mice. Similarly, ex-vivo phenotypic features from mice will be associated to cancer risk, to identify which biomarkers correlate the most with cancer risk. Genetic traits across humans will also be associated to radiation phenotypic features as a function of age and gender.